REMARKS

Finality of Office Action

In response to the Final Office Action, Applicants respectfully request that the Examiner consider the following remarks because the claims as they stand are in condition for allowance.

Examiner's Response to Applicant's Amendments and Arguments

Applicants note that the Office has found Applicants' amendments and arguments submitted on June 2, 2005 to be persuasive. Applicants thank the Examiner for withdrawing the previous rejections.

Claim Rejections - 35 U.S.C. § 103(a)

(a) Rejection of Claims 1-17 and 74-83 over *Southern* in View of *Sorge*

Claims 1-17 and 74-83 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over *Southern et al.* ("*Southern*," WO 95/04160) in view of *Sorge* ("*Sorge*," U.S. Pat. No. 6,607,878). Applicants respectfully traverse this rejection.

As has been acknowledged by the Court of Appeals for the Federal Circuit, the U.S. Patent and Trademark Office ("USPTO") has the burden under section 103 to establish a *prima facie* case of obviousness by showing some objective teaching in the prior art or generally available knowledge of one of ordinary skill in the art that would lead that individual to the claimed invention. *See In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). The Manual of Patent Examining Procedure (MPEP) section 2143 discusses the requirements of a *prima facie* case for obviousness. That section provides as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teaching. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and reasonable expectation of success must be found in the prior

art, and not based on applicant's disclosure.

For at least the reasons set forth in more detail below, in the present case, when *Southern* and *Sorge* are combined they do not teach or suggest all of the features of at least the independent claims 1, 2, 7, 12, and 81-83.

In addition to the above-described defects of the rejection, Applicants respectfully assert that the proposed combination is improper. It has been well established that teachings of references can be combined only if there is some suggestion or incentive to do so. *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). Accordingly, there must be a teaching in the relevant art which would suggest to a person having ordinary skill in that art the desirability of combining the "ladder tag" design of *Southern*, where each discrete oligonucleotide sequence within the mixture is associated with a "spectrum" of mass entities, with the molecular weight "blocks" of colors or other tags of *Sorge*, where certain molecular weight ranges or "gaps" are reserved for post-digestion analysis. There is no teaching in either reference that would suggest the desirability of combining them and, further, knowledge generally available in the art would not motivate one to combine the references. Here, the Office has used impermissible hindsight analysis and, with the invention of the claims in mind, have picked two isolated disclosures in the art and attempted to combine them when there is no motivation to do so. *See In re Fine* 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

Irrespective of the clear lack of motivation to combine the *Southern* and *Sorge* references, the rejection is improper because, even if the teachings of the two references are properly combinable, such combination does not result in Applicants' claimed invention. As provided above, each of Applicants' independent claims recite the following:

> the mixture has a minimum ***mixture coverage complexity of at least 56/N*** or wherein the set of sub-mixtures has a composite mixture coverage

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> complexity of at least 56/N, wherein N represents the number of distinct X-mer precursors in the mixture...
>
> any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight.

(emphasis added). Instead of indicating where these distinct areas are formed in either of *Southern*'s or *Sorge*'s disclosures, the rejection simply generally references portions of *Southern* that refer to "a mixture of 4096 hexanucleotides." *Southern* does not teach or suggest a mixture or set of sub-mixtures of the independent claims that have this specific feature.

Applicants have noted in the specification that:

> As the average length of the X-mer precursor increases, the number of distinct X-mers in the mixtures of this invention also increases and the mixture coverage complexity may decrease. The lower limit of the mixture coverage complexity is equal to a value of 56 divided by the number of X-mers in the mixture. The length of the X-mer precursors can be selected independently for each X-mer precursor.

Specification at 29, lines 1-5. While certain embodiments of *Southern* may suggest mixtures that have this characteristic, *Southern* does not specifically teach or suggest mixtures in general that have this feature. In that *Sorge* does not remedy this deficiency of the *Southern* reference, Applicants respectfully submit that independent claims 1, 2, 7, 12, and 81-83 are allowable over the *Southern/Sorge* combination.

In addition, the Office admits that *Southern* does "not specifically teach any oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight, tags distinguishable by mass spectrometry and kit comprising said mixture of X-mer precursors." *Office Action* at 4, lines 3-5. Indeed, each X-mer precursor of the independent claims possesses a single mass whereas each oligonucleotide in *Southern* is associated with spectra of masses that represent the nucleotide sequence of interest. *Sorge* does not remedy this deficiency of the *Southern* reference either. As noted above, *Sorge* is not properly combinable with *Southern* for at least the reason that *Sorge* is directed to distinguishing fragments, obtained after enzyme cleavage, from one another "on the basis of color." *See, e.g.,*

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Sorge at col. 22, lines 45-67. *See also Sorge* at col. 23, lines 12-16 ("the identity of a particular private nucleotide is associated with the color of a fluorescent tag associated with a particular pb primer. Four different colors could correspond with the four possible bases at a given private nucleotide position. Thus, the pa primer corresponding to each of the four possible nucleotides at a given private sequence position will be included in a separate vessel with a pb primer that includes a particular color label."). *Sorge* also specifically states that:

> The same type of information can be encoded in ***molecular weight 'blocks' of colors*** or other tags that are in multiples of four.... [C]ertain ***molecular weight ranges or 'gaps' are reserved*** for post-digestion analysis. The general concept is that a small set of independently discernible tags can be used to trace the ***alteration in size or molecular weight of a large number of DNA fragments*** cleaved....

Id. (emphasis added). Thus, the fragments and tags of *Sorge* differ from the mixtures in the independent claims in at least two important reasons.

First, claims 1, 2, 7, 12, and 81-83 each recite "any given oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight." The tags of the claims are not "blocks of colors or other tags that are in multiples of four," as described by *Sorge*. Second, the tags of the claims are not limited to those that simply "trace the alteration in size or molecular weight... of DNA fragments," as recited by *Sorge*. Rather, each tag of the instant claims has a discrete molecular weight. Therefore, *Sorge* does not remedy the deficiencies of *Southern* for at least these reasons.

In summary, a *prima facie* for obviousness has not been made against Applicants' claims 1, 2, 7, 12, and 81-83. Therefore, Applicants respectfully submit that each of these claims is patentable over *Southern* and *Sorge* and that the rejection of these claims should be withdrawn.

Because the independent claims are allowable, then for at least this reason, their respective dependent claims 3-6, 8-11, 13, 15-17, and 74-80 are also allowable. There may be other reasons as well why the dependent claims are allowable. For example, claim 74 recites "a kit ... comprising: a. the mixture or set of sub-mixtures of claim 1; and b. an

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enzyme...." Neither *Southern* nor *Sorge* teach or suggest providing a kit that includes the recited mixture or set of sub-mixtures in addition to an enzyme.

(b) Rejection of Claims 1, 3-6, and 74-80 over *Brenner* in view of *Sorge*

Claims 1, 3-6, and 74-80 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Brenner* ("*Brenner*," U.S. Pat. No. 5,654,413) in view of *Sorge*. Applicants respectfully traverse this rejection.

In particular, the Office Action alleges that "Brenner teaches a composition (mixture) of claims 1, 3-5, comprising X-mer precursor having a minimum length of 3 nucleotides..., wherein the mixture the mixture (sic) has at least complexity of at least 56/N, wherein N represents the number of distinct X-mers...." *Office Action* at 5. Applicants disagree. All portions of *Brenner* relied on by the Office have been carefully studies, and they all refer to "an oligonucleotide ***tag***." *See, e.g.*, *Brenner* at col. 3, lines 15-17 ("An oligonucleotide ***tag*** of the invention consists of a plurality of subunits, each subunit consisting of an oligonucleotide of 3 to 6 nucleotides in length.") (emphasis added). In contrast, the independent claims recite "X-mer precursors" and "wherein each tag is covalently linked to at least one X-mer precursor," thus reciting that the X-mer precursor and the tag are not one and the same species. While limitations/features of the specification are not to be imported into the claims, the elements of the claims should be interpreted in light of the specification. In the instant case, the specification recites the following:

> A tag which is useful in the present invention possesses several attributes:
> 1) A tag is distinguishable from all other tags, preferably by mass spectrometry.
> 2) The tag is capable of being detected when present at 10^{-22} to 10^{-6} moles.
> 3) The tag possesses a chemical handle through which it can be attached to a nucleotide or nucleic acid which the tag is intended to identify, preferably uniquely, but not necessarily. The attachment may be made directly to a nucleic acid, or preferably indirectly through a "linker" group, preferably a cleavable linker.

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> 4) The tag is chemically stable toward all manipulations to which it is subjected, including attachment and cleavage from the nucleic acid molecule, and any manipulations of the nucleic acid molecule while the tag is attached to it.
> 5) The tag does not significantly interfere with the manipulations performed on the nucleic acid molecule while the tag is attached to it. For instance, if the tag is attached to an oligonucleotide, the tag must not significantly interfere with any hybridization or enzymatic reactions (e.g., PCR sequencing reactions) performed on the oligonucleotide.

Specification at 34, lines 4-18. In contrast, the X-mer precursors are described in the specification as follows:

> The oligonucleotide precursor (X-mer precursor) reagents of the invention are mixtures of natural X-mer precursors, mass-modified X-mer precursors, or natural and mass-modified X-mer precursors having a minimum length of 3 nucleotides....

Id. at 28, lines 23-25. Thus, the Office has taken the ***tags of Brenner*** and used them to reject the claims based on the ***X-mer precursors of the claims***. *Sorge* does not remedy this deficiency of *Brenner*. For at least this reason, the combination of *Sorge* and *Brenner* does not teach or suggest all features of independent claim 1.

In addition, the Office admits that *Brenner* does "not specifically teach any oligonucleotide sequence in the mixture is attached to preferably a single tag with a discrete molecular weight, tags distinguishable by mass spectrometry." *Office Action* at 6, lines 5-7. *Sorge* does not remedy these deficiencies of the *Brenner* reference either. The fragments and tags of *Sorge* differ from the mixtures in the independent claims for at least two reasons stated above with respect to its combination with the *Southern* reference. For at least the same reasons, the combination of *Brenner* and *Sorge* do not teach or suggest all elements of independent claim 1.

In summary, a *prima facie* for obviousness has not been made against Applicants' claim 1. Therefore, Applicants respectfully submit that this claim is patentable over *Southern* and *Sorge* and that the rejection of these claims should be withdrawn.

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Because independent claim is allowable, then for at least this reason, its dependent claims 3-6, and 74-80 are also allowable. There may be other reasons as well why the dependent claims are allowable. For example, claim 74 recites "a kit ... comprising: a. the mixture or set of sub-mixtures of claim 1; and b. an enzyme...." Neither *Brenner* nor *Sorge* teach or suggest providing a kit that includes the recited mixture or set of sub-mixtures in addition to an enzyme.

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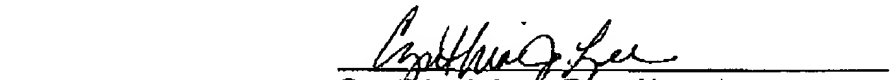
CONCLUSION

In light of the foregoing amendments and for at least the reasons set forth above, Applicants respectfully submit that all rejections have been traversed, rendered moot, and/or accommodated, and that the now pending claims 1-17 and 74-83 are in condition for allowance. Favorable reconsideration and allowance of the present application and all pending claims are hereby courteously requested. If, in the opinion of the Examiner, a telephone conference would expedite the examination of this matter, the Examiner is invited to call the undersigned agent at (770) 933-9500.

Respectfully submitted,



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